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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/803,187	03/18/2004	Thomas Christoph	029310.53299US	5120

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CROWELL & MORING LLP
INTELLECTUAL PROPERTY GROUP
P.O. BOX 14300
WASHINGTON, DC 20044-4300

EXAMINER	
FRAZIER, BARBARA S	
ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/803,187	CHRISTOPH, THOMAS	
	Examiner	Art Unit	
	BARBARA FRAZIER	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-41 and 44-73* is/are pending in the application.

4a) Of the above claim(s) *38,40,41,44-47,52,53 and 58-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,39,48-51,54-57 and 71-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 37-73 are pending in this application.

2. Claims 38, 40, 41, 44-47, 52, 53, and 58-70 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 9/27/07.

3. Claims 37, 39, 48-51, 54-57, and 71-73 are examined.

Claim Rejections - 35 USC § 112

4. The rejection of claim 39 under 35 U.S.C. 112, second paragraph, is withdrawn in view of Applicant's amendment to claim 39 and arguments that one or more of either set of compounds is present in the form of a pure enantiomer or pure diastereoisomer.

Claim Rejections - 35 USC § 103

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. The rejection of claims 37, 48-51,54, 57 and 71-73 under 35 U.S.C. 103(a) as being unpatentable over Chutka et al. ("Urinary Incontinence in the Elderly: Drug Treatment Options," 1998, Drugs, Volume 56, Number 4, Pages 587-595 and cited by Applicant), in view of Buschmann (US Patent 5,811,582} and Andersson et al ("The

pharmacological treatment of urinary incontinence," 1999, British Journal of Urology International, 84:923-947 and cited by Applicant) is withdrawn in view of Applicant's arguments specifically directed to Buschmann '582, i.e., that Buschmann '582 does not teach the compounds of the claimed invention according to formula I as active pharmaceutical ingredients, but rather as intermediates for forming pharmaceutical active ingredients. It is noted that Applicant's arguments regarding the references of Chutka et al and Andersson et al are addressed in response to the rejection newly applied, below.

7. The rejection of claims 55 and 56 under 35 U.S.C. 103(a) as being unpatentable over Chutka et al in view of Buschmann '582 and Andersson et al, and further in view of Buschmann et al (US Patent 6,248,737) is deemed moot in view of the new rejection below.

8. The following rejection is newly applied:

9. Claims 37, 39, 48-51, 54-57, and 71-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chutka et al. ("Urinary Incontinence in the Elderly: Drug Treatment Options," 1998, Drugs, Volume 56, Number 4, Pages 587-595 and cited by Applicant), in view of Buschmann (US Patent 6248,737) and Andersson et al ("The pharmacological treatment of urinary incontinence," 1999, British Journal of Urology International, 84:923-947 and cited by Applicant).

The claimed invention is drawn to a composition comprising an admixture of an analgesic and an anti-muscarinic agent (see claim 37); Applicants have elected (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride as

the analgesic (see claims 37, 39, 48-51, and 54-57). The antimuscarinic agent is selected from the group consisting of atropine, oxybutinin, propiverine, propantheline, emepronium, trospium, tolterodine, darifenacin and α, α,-diphenylacetic acid 4-(N-methylpiperidyl) ester, duloxetine, imipramine and desmopressin (claim 37).

Chutka et al teach that both anticholinergic drugs (i.e., antimuscarinic agents) and opioids can decrease the contraction of the detrusor by impairing the contractility of the detrusor and potentially lead to urinary retention (see, e.g., page 593, third paragraph, and Table 1).

Chutka et al do not specifically teach the combination of an analgesic such as (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride and an antimuscarinic agent such as one of those recited in claim 37.

Buschmann ‘737 teach 1-phenyl-3-dimethylaminopropane compounds with an analgesic effect, which are suitable or the treatment of severe pain without giving rise to the side effects which are typical of opioids, and which do not exhibit the side effects, for example nausea and vomiting, which occur during treatment with the opioid tramadol in some cases, and which has a significantly enhanced analgesic effect compared with that of tramadol (col. 1, lines 52-65). Buschmann ‘737 teaches a method of making and separating the (+) enantiomer of (2R, 3R)- 1-dimethylamino-3-(3-methylphenyl)-2-methylpentan-3-ol (Example 1, column 6, line 23 to column 7, line 61). Buschmann '737 teaches that the (+) enantiomer of (2R, 3R)-1-dimethylamino- 3-(3-methylphenyl)-2-methylpentan-3-ol is a superior analgesic compared to the racemic mixture or (-) enantiomer (column 23, Table).

Andersson et al teach pharmaceutical substances that are known to treat urinary incontinence (Title) and include anti-muscarinic (i.e., anticholerinergic) agents such as atropine, propantheline, emepronium, trospium, tolterodine, darifenacin, oxybutynin and propiverine (pages 924 and 925, table 2). Andersson et al teach that one such anti-muscarinic agent, oxybutinin, has well documented efficacy in the treatment of detrusor hyperactivity, is available in various forms, and is probably the drug of first choice in patients with detrusor hyperactivity (page 930, column 2, third and fifth full paragraphs).

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to combine an admixture of (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride and an antimuscarinic agent; thus arriving at the claimed invention. One skilled in the art would be motivated to do so, with a reasonable expectation success, for the following reasons: First, one skilled in the art would be motivated to combine an opioid and an anticholinergic agent, since both are known to impair detrusor contraction, as taught by Chutka et al. It is prima facie obvious to combine two compositions, each of which is taught by the prior art, to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. See MPEP 2144.06. Second, one skilled in the art would be motivated to substitute (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride for an opioid, since the aminopropane compound has an enhanced analgesic effect compared to an opioid (and therefore would be reasonably expected to have the same or improved efficacy in relaxing bladder muscles as well) but without the negative side effects, as taught by Buschmann ‘737. Third, one skilled in

the art would be motivated to select one of the antimuscarinic agents listed in claim 37 because a number of said compounds are known to be effective as antimuscarinic agents, and one of them (oxybutinin) is even known as the "drug of choice", as taught by Andersson et al.

Regarding claims 71 and 72, Andersson et al teach compounds such as oxybutinin as known antimuscarinic agents (see pages 924 and 925, Table 2, and page 930).

Regarding claim 73, Buschmann '737 teaches that the analgesics are administered with pharmaceutically suitable auxiliary substances (see col. 5, lines 48-67).

Response to Arguments and Data in Specification

10. Applicant's arguments filed 2/11/09 have been fully considered but they are not persuasive.

Applicants first argue that the Chutka et al article is silent on the use of a combination of opioids and anticholinergic drugs (i.e., antimuscarinic drugs). This argument is not persuasive because Chutka et al do teach that both opioids and anticholinergic drugs impair detrusor contraction, and it is prima facie obvious to combine two compositions, each of which is taught by the prior art, to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. See MPEP 2144.06.

Applicants also argue that the data in the present application demonstrates a synergistic effect with the combination of (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride and oxybutinin over each compound separately (see pages 20 and 21 of Applicant's response filed 2/11/09).

This argument is not persuasive. The data in Applicant's specification has been fully considered, but is not deemed persuasive for overcoming the rejection. The data in the Table on page 50 of Applicant's specification shows that 0.1 mg/kg of compound A was administered separately, and 0.03 mg/kg of Compound B was administered separately, but in the combination, 0.1 mg/kg of Compound A and **0.3 mg/kg of Compound B** were administered together (see page 50; emphasis added). Therefore, one skilled in the art would reasonably expect a much greater inhibition when **10 times** the amount of compound B is used in the combination. If this is a typographical error, and only 0.03 mg/kg of Compound B were used in the combination, the data is still not persuasive for overcoming the rejection, since the data is not commensurate in scope with the claims, as the data is limited to a single amount of each compound, while the claims are drawn to the compounds in any amount. Furthermore, the data is also limited to a single antimuscarinic agent (oxybutinin), while the elected claims are drawn to any antimuscarinic agent from the list in claim 37.

Applicants also argue that the Andersson et al article does not teach or suggest administering a combination of opioids and anticholinergic drugs (i.e., antimuscarinic drugs), or that a combination of opioid and an antimuscarinic drug might result in a synergistic effect.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants also argue that the '737 patent is silent on the use of the compound of formula I for treating an increase urge to urinate or urinary incontinence, but only teaches treating severe pain (see page 24 of Applicant's response filed 2/11/09).

This argument is not persuasive because the rejection is based on a combination of references, including Chutka and the '737 patent, and not the '737 patent individually. Since Chutka teaches that opioids, which are known analgesics, have direct effects on the bladder muscle, and the '737 patent teaches that its compound is a superior analgesic to opioids, one skilled in the art would reasonably expect the compound of the '737 patent to also have an analgesic effect on the bladder muscle, thereby also impairing detrusor contraction. It is further noted that the claims are drawn to compositions, and are not limited to a particular method of use.

Applicants also argue that the claimed combinations are active at doses which are "significantly lower than those which might reasonably been expected".

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the claimed compositions at particular doses) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from

the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Additionally, one skilled in the art would reasonably expect that a lower dose would result in fewer side effects, since less of the drug is being given to the patient.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BARBARA FRAZIER whose telephone number is (571)270-3496. The examiner can normally be reached on Monday-Thursday 9am-4pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BSF

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611